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NEUROCRITICAL CARE SOCIETY

BRIEF COMMUNICATION

One-Year Outcomes in Disorders of Consciousness Associated with COVID-19

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Patients with severe coronavirus disease 2019 (COVID-19) may suffer prolonged disorders of consciousness (COVID-DoC) that are unexplained by structural brain injury or sedative medications [1–3]. We and others have found that patients typically recover consciousness after COVID-DoC up to several weeks after sedative medications are withdrawn [1–3]. However, the recovery trajectory and long-term prognosis of COVID-DoC remain unclear, complicating critical decisions about the withdrawal of life-sustaining treatment. We previously reported a case of patient with COVID-DoC who, by a year after his hospitalization, demonstrated a nearly complete cognitive recovery, though he remained immobilized by severe myoneuropathy [4]. Because long-term recovery from COVID-DoC has not yet been prospectively studied, it is unclear to what extent this case typifies COVID-DoC recovery. Here, we report the 1-year outcome data from a prospective COVID-DoC cohort to inform the long-term prognosis of this condition.

We previously launched a prospective, institutional review board–approved study to investigate the natural history of COVID-DoC [1]. After consecutively screening 1,105 patients with COVID-19 admitted to Massachusetts General Hospital between July 2020 and March 2021, we identified and enrolled 12 with a disorder of consciousness unexplained by brain injury on computed tomography imaging or sedation (as evaluated by investigators trained in neurocritical care [DF and BLE]). Surrogates provided informed consent for enrollment. We monitored neurologic function using the Disability Rating Scale (DRS) and the Glasgow Outcome Scale Extended (GOSE) at hospital discharge and at 3, 6, and 12 months following hospital discharge via telephone interviews [5, 6]. Additional details of this patient cohort are reported previously [1] and in Supplementary Table 1.

All patients in this cohort recovered consciousness, though four later died of medical complications during the hospitalization. At hospital discharge, the eight surviving patients remained disabled, requiring inpatient care. By 3 months post discharge, five lived at home with mild physical disability and three remained in an inpatient facility. By 6 months, six lived at home with minimal disability and two (patients 2 and 3, as named previously [1]) remained in an inpatient facility.

Given their clinical implications, we previously published these findings, but continued to monitor recovery at 1 year post discharge as originally planned (ClinicalTrials.gov protocol NCT04476589), which we report here.

Recovery plateaued after 6 months, with neurologic function remaining similar between 6 months (median GOSE score 4 [interquartile range (IQR) 4–5], median DRS score 3 [IQR 3–5]) and 1 year (median GOSE score 4 [3–6], median DRS score 6 [IQR 2–7]) post discharge (Fig. 1). At 1 year, six patients remain at home with no cognitive deficits revealed by the GOSE or DRS but ongoing mild physical sequelae of critical illness, including weakness (e.g., drop foot, difficulty donning shoes), visual deficits (e.g., monocular blindness, diplopia), and fatigue. Three ambulate independently, two occasionally use a cane, and one used a scooter at baseline. Two returned to work, one cannot work because of fatigue, and three did not work at baseline.

In contrast, at 1 year post discharge, patients 2 and 3 remain more severely disabled in inpatient facilities. During their initial hospitalization, both had prolonged unconsciousness following the withdrawal of intravenous sedation (25 and 18 days, respectively, among the longest of the cohort) and quadriplegia attributed to severe sensorimotor polyneuropathy (confirmed with nerve

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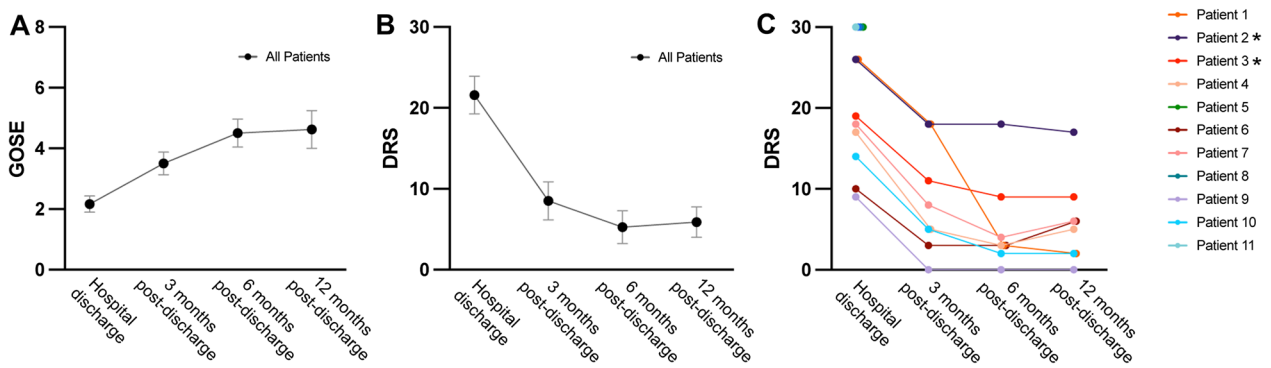

Fig. 1 Recovery of neurologic function after coronavirus disease 2019–related disorders of consciousness (COVID-DoC). The Glasgow Outcome Scale Extended (GOSE) (**a**) and Disability Rating Scale (DRS) (**b**) scores plateau after 6 months following hospital discharge. Higher scores on the GOSE and lower scores on the DRS reflect less disability. Scores are expressed as means, and error bars represent standard error of the mean. DRS scores for each patient are also represented (**c**). Outcomes for the four patients who died during the hospitalization are not represented beyond hospital discharge. The two patients with persistent severe disability (patients 2 and 3) are marked with asterisks.

conduction studies). Electromyography additionally revealed myopathic findings in patient 3, and creatine kinase levels rose to 3699 and 1,144 U/L in patients 2 and 3, respectively. Otherwise, they were comparable with others in the cohort, with similar ages (62 and 43, respectively), comorbidities, intubation durations, and sedative dosages (Supplementary Table 1). Although brain magnetic resonance imaging revealed either leukoencephalopathy or microhemorrhages in most patients (82%), such findings were either mild or absent in patients 2 and 3 (Supplementary Table 1).

Following hospital discharge, both demonstrated persistent, but gradually improving, encephalopathy; they are now partially oriented, following simple commands, and engaging in simple conversation. The encephalopathies have been intermittently attributed to medical complications following hospital discharge, such as recurrent bacteremia, but have persisted after such complications have resolved. Patient 3 also demonstrated emotional lability, frequently crying without provocation, which has improved. Their weakness remains severe but has also improved; though both are unable to ambulate, they now have antigravity strength in their upper extremities.

The etiology of their polyneuropathies is uncertain. Though initially attributed to critical illness, both subsequently underwent lumbar punctures that revealed cytoalbuminologic dissociation, and patient 3 exhibited nerve root enhancement on lumbar spine magnetic resonance imaging, suggesting a possible inflammatory etiology (an association between COVID-19 and inflammatory polyneuropathies has been suspected [7], though alternative etiologies, such as microvascular disease, cannot be excluded). Patient 2 received intravenous immunoglobulin at 1 g/kg every 3 weeks, which was felt to accelerate her recovery. Patient 3 received one course of intravenous immunoglobulin at 2 g/kg over 3 days, which, after 2 months, was not felt to be therapeutic and thus was discontinued.

These two cases, as well as our previously reported case [4], suggest a possible association between prolonged COVID-DoC and severe polyneuropathy, which may result in protracted cognitive and physical disability. The nature of this association remains unclear. Possible explanations include (1) prolonged COVID-DoC increases susceptibility to critical illness neuropathy, (2) quadriplegia mimics COVID-DoC by masking evidence of command-following in the extremities, and (3) COVID-19 triggers an inflammatory process in both the central and peripheral nervous systems.

These 1-year outcome data provide additional insight into long-term recovery from COVID-DoC. First, neurologic recovery tends to plateau after 6 months. Second, for most patients who survive to hospital discharge (75%), this plateau typically entails mild physical sequelae of critical illness, such as fatigue and weakness. And third, for a minority of patients (25%) with prolonged COVID-DoC and severe polyneuropathy, more severe cognitive and physical disability may persist. There are limitations to this study; it remains a relatively small cohort, dedicated cognitive assessments (beyond the GOSE and DRS) were not performed, and it remains unknown whether these recovery trajectories are specific to COVID-DoC (i.e., whether they differ from those with similarly prolonged critical illness unrelated to COVID-19). Nonetheless, we hope that these additional insights help refine the prognosis of COVID-DoC and inform future investigation.

Supplementary Information
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Author contributions
David Fischer and Brian Edlow conceived the study and wrote the manuscript.

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Conflicts of interest
David Fischer reports no conflicts of interest. Brian Edlow reports no conflicts of interest.

Ethical approval/informed consent
This article adheres to ethical guidelines. Informed consent was obtained from all patients via surrogate decision-makers.

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